Neuroscience

Exposure to false cardiac feedback alters pain perception and anticipatory cardiac frequency

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Abstract

The experience of pain, like other interoceptive processes, has recently been conceptualized in light of predictive coding models and the free energy minimization framework. In these views, the brain integrates sensory, proprioceptive, and interoceptive signals to generate probabilistic inferences about upcoming events, which heavily shape both the state and the perception of our inner body. Here we ask whether it is possible to induce pain expectations by providing false faster (vs. slower) acoustic cardiac feedback before administering electrical cutaneous shocks, and test whether these expectations will shape both the perception of pain and the body's physiological state toward prior predictions. Results confirmed that faster cardiac feedback elicited pain expectations that affected both perceptual pain judgments and the body's physiological response. Perceptual pain judgments were biased towards the expected level of pain, such that participants illusorily perceived identical noxious stimuli as more intense and unpleasant. Physiological changes mirrored the predicted level of pain, such that participants' actual cardiac response in anticipation of pain stimuli showed a deceleration in heart rates, coherently with the well-known orienting cardiac response in anticipation of threatening stimuli (Experiment 1). In a control experiment, such perceptual and cardiac modulations were dramatically reduced when the feedback reproduced an exteroceptive, instead of interoceptive cardiac feedback (Experiment 2). These findings show for the first time that cardiac feedback manipulation can be conceptualized in terms of an interoceptive inference that modulates both our perception and the physiological state of the body, thereby actively generating the interoceptive and autonomic consequences that have been predicted.

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In this **valuable** study, Parrotta et al. showed that it is possible to modulate pain perception and heart rate by providing false heart rate (HR) acoustic feedback before administering electrical cutaneous shocks. The evidence supporting the claims of the authors is rather **solid**, although what they consider an interoceptive signal is not necessarily supported as such by the results. In this regard, including a larger number of trials per participant, increasing the sample size, and adding a measure of actual pain perception after its induction would have strengthened the study. Although mechanisms and some alternative explanations for this effect remain to be addressed, the work will nonetheless be of interest to neuroscientists working on predictions and perception, health psychologists, pain researchers, and placebo researchers.

Introduction

Far more complex than the mere transmission of nociceptive inputs, pain is a component of the interoceptive system (Craig, 2003). It is defined as a protective experience that can occur even in the absence of physical harm (Loeser & Treede, 2008) and is permeated by all the available sources of information, including sensory, emotional, cognitive, and social components as well as prior information and what one expects to happen (Atlas & Wager, 2012; Tracey, 2010; Williams & Craig, 2016). While the last decades provided important advances in the understanding of pain, developing an overarching theory that accounts for all the dimensions of pain still remains challenging (for a full discussion, see Moayedi and Davis, 2013).

Current views propose predictive processing models as a suitable candidate to account for the multifaceted experience of pain (Büchel et al., 2014; Kiverstein et al., 2022; Song et al., 2019, 2021). Interoceptive inference and the Embodied Predictive Coding frameworks (for a full discussion see Barrett, 2017; Barrett and Simmons, 2015; Pezzulo, 2014; Seth, 2013; Seth and Friston, 2016) conceptualise the brain as an active generator of inferences, which constantly updates an internal model of both the internal and the external world and attempts to fit it with incoming inputs through a process of Bayesian hypothesis testing and revision. Interoceptive sensations are thought to be derived by the integration of different sources of information into an expectation of the body's upcoming changes, which are kept in check by the actual state of the body (Barrett & Simmons, 2015). However, people's predictions do not always mirror the reality, but they can be often inaccurate, leading to a gap between the expected and the actual present state. The goal of inferential processes is to reduce the difference between one's internal models and the actual interoceptive input, thus converging towards the *brain's best guess* about the body's state (Ainley et al., 2016; A. Seth et al., 2012; A. K. Seth & Friston, 2016).

An important feature of these accounts is that the difference between one's internal models and the actual sensory data can be minimized not only by updating internal models to better fit the data (i.e., perceptual inference), but also by performing actions, changing bodily states themselves (i.e., active inference) (for a full discussion, see Friston, 2010, 2005; Parr et al., 2022). For example, an expectation of a threatening, painful stimulus could be realised both by making the painful stimulus *appear* more painful than it really is, thereby fitting one's internal model to bodily reality, or by *actually* modulating the state of the body and shape the physiologic response to pain towards previous predictions, for example by engaging autonomic reflexes (e.g., typical decrease in the heart rate in relation to pain anticipation, e.g., Bradley et al., 2008, 2005; Colloca et al., 2006; Lykken et al., 1972; Taggart et al., 1976; Tracy et al., 2017).

There is suggestive evidence for both components in the extant literature on pain. The assumption that prior information modulates pain perception underlines decades of work on placebo and nocebo effects (i.e., the expectation-effect; Crombez et al., 1998; Keltner et al., 2006; Petrovic and Ingvar, 2002; Price et al., 1999; Wager, 2005; Wager et al., 2004). On a neuronal level, expecting pain alters the neural mechanisms in pain-processing regions, thought to reflect a combination of nociceptive inputs and top-down information (Atlas et al., 2010; Keltner et al., 2006; Koyama et al., 2005; Wiech et al., 2008), even at a very early stage of processing (Eippert et al., 2009; Geuter & Büchel, 2013). Moreover, such changes can persist – or even grow over time – in the absence of disconfirming evidence (Atlas et al., 2010; Colloca et al., 2010; Craggs et al., 2008; Jepma & Wager, 2015; Koban & Wager, 2016; Montgomery & Kirsch, 1997; Vase et al., 2005, 2011), turning pain experience into potentially a self-fulfilling prophecy (Jepma et al., 2018).

As for the assumption that unfulfilled predictions can be resolved by changing the state of the body and engaging autonomic reactions, there is evidence that prior pain expectations, and pain itself, modulate physiological responses. Expecting pain induces augmented activity in the sympathetic system (e.g. increases in blood pressure and skin conductance) to prepare potential avoidance responses (Barlow et al., 1996; Oka et al., 2007; Tousignant-Laflamme & Marchand, 2006; Yang et al., 2003), as well as a characteristic decrease in heart rate to promote orienting responses, attention and sensory processing (Bradley et al., 2008, 2005; Colloca et al., 2006; Lykken et al., 1972; Taggart et al., 1976; Tracy et al., 2017; for a full discussion, see Skora et al., 2022)

Collectively, these findings support the idea that the experience of pain relies on top-down predictive mechanisms, which affect not only the subjective perception of pain, but also its neural and bodily correlates. However, in previous work pain expectations were typically induced by exteroceptive cues (e.g., visual, Wiech et al., 2014; Jepma et al., 2019; auditory, Colloca et al., 2006; Atlas et al., 2010), neglecting the role of interoceptive sources of information within the inference. Among such streams, the activity of the heart appears to be tightly linked with the experience of pain, probably due to a close integration of the pain system and the neural network involved in cardiovascular regulation ((Bud) Craig, 2003; Craig, 2003, 2008). For example, pain-related evoked potentials and nociception can be modulated over the cardiac cycle (Edwards et al., 2001, 2002, 2008; Martins et al., 2009; McIntyre et al., 2006), and either the anticipation or the response to pain stimuli is associated with changes in heart rates (Colloca et al., 2006; Mischkowski et al., 2018; for a review, see Kyle and McNeil, 2014). Moreover, when estimating their cardiac frequency, people's predictions draw upon the level of threat (i.e., pain) associated with upcoming events (Parrotta, 2022), reflecting the (fictitious) belief that threat expectations lead to an increase in heart rates. Even though anticipating pain typically goes along with decreases in heart rates (the well-known orienting response Bradley et al., 2008, 2005; Colloca et al., 2006; Lykken et al., 1972; Taggart et al., 1976; Tracy et al., 2017), people may therefore illusorily perceive a higher cardiac frequency when expecting painful stimulation (Parrotta et al., 2022).

The tight coupling between heart rates changes and pain experience suggests that it should be possible to modulate the experience of pain by manipulating *interoceptive cardiac* feedback, that is, by misleading people into believing that their heartrate is increasing in anticipation of a noxious stimulus. Under predictive architectures, persuading one's internal model towards the fictitious evidence of increased heart rates (i.e., faster cardiac feedback manipulation) would potentially induce consequent changes both in *pain perception* (i.e., perceptual inference) and in the *actual state of the body* (i.e., active inference). Specifically, the former process would correspond to an interoceptive illusion of increased pain (where "illusion" is used in the same sense as in bodily illusions, e.g., Ferri et al., 2013; Tsakiris et al., 2011), whereas the latter would correspond to physiological and autonomic adaptations to the predicted level of pain. While it has been consistently reported that exteroceptive cues induce predictions about pain, it is

currently unknown whether a cardiac feedback manipulation that renders interoceptive streams more similar to those expected in pain conditions would produce an interoceptive illusion of pain and ensuing autonomic adjustments - as hypothesized by interoceptive inference and embodied predictive coding theories. To test this hypothesis, Experiment 1 provided participants with auditory cardiac feedback, via headphones, that was either congruent with their heartbeat frequency, or incongruent with it (i.e., faster or slower) before the administration of a noxious electrical stimulation, while their ECG was recorded. Once the pain stimulus was administered, subjects were asked to rate the intensity and unpleasantness of the painful stimuli.

We predicted, first, that the exposure to faster vs. slower cardiac feedback induces expectations of increased levels of pain, such that noxious stimuli are felt and reported as more unpleasant and intense. Second, expectations of threat induced by the faster feedback should be fulfilled through parasympathetic reflexes, such that participants' real heartrates decrease over the exposure to the incongruent faster, compared to the slower cardiac feedback, in line with the well-known orienting cardiac response when expecting threat or pain (Bradley et al., 2008, 2005; Colloca et al., 2006; Lykken et al., 1972; Taggart et al., 1976; Tracy et al., 2017; for a full discussion, see Skora et al., 2022). To rule out that potential modulations in participants' pain perception and cardiac state were merely associated with the frequency of the feedback, rather than an heartbeat, Experiment 2 replicated the design in a second group of participants, with the only difference being that the congruent or incongruent feedback would not be a heartbeat tone, but an unrelated exteroceptive stimulus. We predicted that as participants would have no expectation that such an external stimulus signals a preparation for a threatening, painful stimulus, variations in the rate of this exteroceptive stimulus should lead to no (or less) perceptual and cardiac changes.

If confirmed, the results would provide the first evidence that predictive processes are generated by the simulation of interoceptive streams (i.e., cardiac feedback manipulation), influencing not only our perception of pain but also its heart-related physiological response: two changes that jointlyminimize the discrepancy between the expected and the actual homeostatic (interoceptive) state. This evidence would corroborate the assumption that predictions originate along the embodied multisensory sphere, by orchestrating multiple sources of information (i.e., interoceptive) within the inference. Ultimately, the results may provide important insights into how the experience of pain is actively built in light of predictive processes, shedding new light into the understanding of pain-related pathologies in terms of chronic *aberrant predictions*, as already hypothesized for other dysfunctional conditions (Corlett et al., 2019; Gagne et al., 2018; Lissek & van Meurs, 2015; Powers et al., 2017; Series, 2019), laying the groundwork for new avenues for the future comprehension of pain and its treatment.

Experiment 1

Experiment 1 tests whether false cardiac feedback of an accelerated (i.e., faster), relative to a decelerated (i.e., slower) heartrate alters both pain perception and the cardiac anticipatory response to noxious stimuli.

Methods

Participants

A sensitivity analysis with G*Power 3.1 (Faul et al., 2007) showed that a sample size of 34 provides .90 power to detect effects with Cohen's d =0.57 (SESOI of δ = 0.34).Thirty-four participants (mean age 25.11, *SD*= 2.94, 21 women) took part in the experiment, recruited from

Gabriele D'Annunzio University and the wider community. All were right-handed with normal or corrected-to-normal vision. Exclusion criteria for taking part were self-reported chronic and acute pain, neurological disease, serious cardiovascular disease (i.e., any type of disease involving the heart or blood vessels that might result in life-threatening medical emergencies, e.g., arrhythmias, infarct, stroke), or conditions that could potentially interfere with pain sensitivity (e.g. drug intake or skin diseases). Participants were asked to either not drink coffee or smoke cigarettes in the 60 minutes preceding the experiment. All gave written informed consent, were unaware of the purposes of the study, and were fully debriefed about it at the end of the experiment. Ethical approval from the local ethics board was obtained. One participant was excluded as, at the end of the experiment, they declared to suffer from a cardiac defect that made them realize the manipulation of the cardiac feedback.

Apparatus

Painful stimuli were electrical pulses delivered using a constant-current electrical stimulators (Digitimer DS7A) controlling a pair of neurological electrodes attached on the phalanx of the middle finger of the participant's left hand, which provide a precise constant current, isolated stimulus, controllable in pulse duration and amplitude. The intensity of the electrical stimuli (2 ms) was kept fixed over the experiment and it was established during a calibration phase before the experiment.

Cardiac recording was performed by a Biopac MP 160 system (Biopac Systems Inc., USA). ECG was recorded continuously from two electrodes attached to the lower ribs and one over the right mid-clavicle bone (reference electrode). The ECG signal was sampled at 2 kHz with the Biopac Acqknowledge 3.7.1 software (Biopac Systems Inc., USA) according to the manufacturer guidelines. ECG signal was then fully analysed in MATLAB (R2020a). The tone used for the creation of the feedback was the sound of a single heartbeat, gathered from *https://freesound.org* and manipulated in Audacity. The feedback audio was then created in MATLAB(R2020a), repeating the single heartbeat sound according to the desired frequency (see *Procedure*).

Stimulus presentation was controlled through E-Prime (Psychology Software Tools Inc., Pittsburgh, USA), which interfaced with the pain stimulators and the Biopac system via a parallel port.

Procedure

Upon arrival at the lab, participants were briefed by the experimenter. After providing consent, theywere placed in a comfortable chair, and the ECG electrodes were applied after cleaning the skin. To increase the ambiguity, and thus predictive influences acting on the pain stimulus (Yon & Frith, 2021), the intensity of the noxious input varied between five intensities, which were identified for each participant in an initial calibration session. To do so, participants were informed that they would undergo a psychophysical calibration procedure to determine their subjective response to increasing stimulus intensities. They were comfortably seated with their left hand placed on a table. Before electrodes were placed, the skin was cleaned with alcohol to reduce impedance. The first stimulus was delivered at a low intensity, which is below the threshold for pain perception in most people. The intensity increased in a ramping procedure up to a maximum of five volts. Participants verballyrated the pain intensity for each stimulus using a 0-100 Numerical Pain Scale (NPS).

Following previous research (Atlas et al., 2014; Colloca et al., 2006; Hird et al., 2019) a pain intensity rating of NPS 20 denoted "just painful", NPS 50 denoted "medium pain", and NPS 80 marked the point at which the stimulus was "just tolerable". We identified a 'low' pain level of 10, a 'low-medium' pain level of 30, a 'medium' pain level of 50, a 'medium-high' pain level of 70, and a 'high' pain level of 90. Level 100 was considered the point where the participant did not wish to

experience a higher stimulation level in the experimental session and was not used. We repeated this procedure three times and computed the average stimulus intensities over these three repetitions corresponding to NPSs 10, 30, 50, 70, and 90.

Participants then underwent a pre-experiment test procedure: stimulus intensities corresponding to their pain intensity ratings NPS 10 to 90 were delivered in a pseudo-randomized order four times and participants were instructed to identify the intensity of each pulse. Participants had to correctly identify 75% of stimulus intensities to continue to the main experiment. If they did not achieve this in the test procedure, the intensities were adjusted, and the test was repeated until participants correctly identified 75% of stimulus intensities (Hird et al., 2019). Participants were excluded if their level of correlation between their ratings of the five levels of the nociceptive stimulus intensities within the baseline phase was below r=0.75, suggesting insensitivity to the varying nociceptive degrees of the electrical stimulus, and an essentially flat response profile. No participants were excluded with this criterion.

Having established the individual levels of intensity for each stimulation, participants were informed that their task was to rate the intensity and unpleasantness of nociceptive stimulations. We carefully described the distinction between intensity and unpleasantness ratings using the standard language developed by Price et al. (1989), emphasizing that pain intensity and unpleasantness should be rated independently.

The experiment started with a no-feedback session in which participants' heartrate in anticipation of the shock (measured with ECG) and perceived level of pain (measured with Numeric Pain Scale and Likert scale) were assessed. These measures were used to normalize our dependant variables for our analysis (see *Data analysis*), and to create the acoustic false feedback stimuli to be used as feedback in the experimental session.

Participants were seated in front of the computer, with the ECG electrodes attached, their left hand placed on the table with the electrodes of the cutaneous electrical stimulation fixed on the phalanx of the middle finger, and their right hand placed on the mouse, ready to start the task. The ECG was recorded for the entire session.

Each trial of the no-feedback phase started with the presentation of a fixation cross appearing on the screen. After 60 seconds, a single electrical shock was administered, randomly varying the level of intensity in each trial – as established in the previous calibration phase (i.e., NPS 10, 30, 50, 70, and 90). After each stimulation, participants first rated the intensity of the painful stimulus (instruction: "How intense was the painful stimulation?") on a continuous Numerical Pain Scale (NPS) appearing on the screen, from 0 ("not at all painful") to 100 ("extremely painful"). They then rated the unpleasantness of the painful stimulus (instruction: "How unpleasant was the painful stimulation?") on a 5-point Likert scale (1=no pain, 2=weak, 3=moderate, 4=severe, 5=extremely severe). The two scales were both presented on the screen in succession, and participants expressed their perceptual judgments through a mouse click on the scales. Between trials, a pause screen was shown for 45 seconds, in order to avoid the subsequent trial to be contaminated by the heart rate response to the shock. Then, a new screen appeared with the instructions to press the spacebar to start the new trial.

The no-feedback phase comprised 10 trials, after which participants were asked to wait and rest for 15 minutes before participating in the second experimental phase. This time was used by the experimenter to prepare the acoustic stimuli for use in the second session for each participant. For this purpose, we assessed the individual mean heart rate over the anticipation of the painful stimulus by measuring the mean R-R intervals of the ECG for the whole 1-min interval preceding the shock, and by transforming them into frequency (1/R-R, Colloca et al., 2006). The congruent feedback consisted of tones of heartbeats reproduced at the same individual HR frequency recorded over the no feedback phase. The incongruent faster and slower feedback consisted of

tones of heartbeats reproduced at a frequency corresponding to an R-R interval obtained by either reducing or increasing the length of the original mean R-R interval over the no-feedback phase of 25%, respectively. Specifically, the incongruent acoustic feedback always started at a frequency rate that reproduced the individual heartrate recorded over the no feedback phase, to then gradually increase or decrease the R-R length according to whether the feedback was slower or faster, respectively.

In the feedback phase participants were informed that their task was similar to the previous no-feedback procedure, namely, to rate the intensity and unpleasantness of pain stimuli. Crucially, they were also informed that over the 60 seconds preceding the administration of the shock, they were exposed to acoustic feedback, which was equivalent to their ongoing heart rate. This phase consisted of 18 trials of 60 seconds (i.e., fixation) each, after which the electrical shock was administered, randomly varying its intensity in each trial (i.e., NPS 30, 50, and 70). Each level of intensity of the nociceptive stimulus was associated with one of the three different types of acoustic feedback, one congruent and two incongruent (i.e., slower and faster) with the participant's heart rate recorded over the anticipation of the shock in the previous no-feedback phase. As in the previous no-feedback phase, participants' individual mean heart rate in anticipation of the painful stimulus (i.e., ECG) and the perceived intensity of pain (i.e., NPS and Likert scale) were assessed. The order of the experimental conditions (i.e., congruent, slower and faster) was randomly generated for each individual participant by a web-based computer program (*www.randomization.com (http://www.randomization.com/)*)

Body Perception Questionnaire

After the experiment, all participants completed the Body Perception Questionnaire (Short form BPQ-SF) (Poli et al., 2021), to investigate whether either perceptual or autonomic modulation as induced by our task would be predictive of self-reported measures of bodily awareness and reactivity.

The Body Perception Questionnaire is a 22-item self-administered questionnaire that assesses awareness and reactivity of the autonomic nervous system, that is, the subjective ability to perceive bodily states and bodily reactions to stress. High scores on the BPQ reflect high awareness of internalbodily signals (i.e., high interoceptive sensibility) and high perceived reactivity of the visceral nervous system. Items ask participants to rate, on a 5-point scale (from 1 = *never* to 5 = *always*), the frequency with which they feel aware of bodily sensations (e.g., body awareness subscale "My mouthbeing dry"), experience supradiaphragmatic reactivity (e.g., supradiaphragmatic reactivity subscale "I feel shortness of breath"), and subdiaphragmatic reactivity (e.g., subdiaphragmatic reactivity subscale reactivity subscale "I have indigestion"). In this work, we focus on the body awareness and supradiaphragmatic reactivity subscales, given our specific focus on attention to the heart (Petzschner et al., 2019).

Data Analysis

Pain ratings (i.e., Likert and NPS ratings) collected in the feedback phase were normalized to the no-feedback phase in order to control for inter-individual variability in pain perception, as established by previous research (Bartolo et al., 2013; Cecchini et al., 2020; Riello et al., 2019) following the formula: Normalized value = (X-bX)/bX, where X represents the mean value of each measure assessed in the experimental feedback phase and bX the mean value of the measure calculated over the no-feedback phase. The same procedure of normalization was coherently applied to measures of the heart rate, recorded with the ECG in both the experimental feedback and no-feedback phase. We did not have specific hypotheses about how the different levels of noxious stimulus intensity affect the perceptual illusion, as we used them only to generate variability, thus all dependent variables were averaged across the three intensities (i.e., NPS 30, 50, and 70).

To provide a directional measure of whether the exposure to the faster and slower cardiac feedback induced similar or contrasting changes in actual heart rate and pain ratings, the mean value of all our dependant variables obtained over the exposure to the congruent feedback phase was subtracted to the scores acquired in both the incongruent faster and incongruent slower phase. This enabled us to obtain a variation rate (i.e., delta, Δ) for all our variables of interest (Δ pain intensity ratings, Δ pain unpleasantness rarings, Δ heart rate). Analysis was conducted on these values, allowing us to show whether the exposure to the false feedback manipulation (i.e., incongruent faster and slower feedback), relative to the exposure to the veridical (i.e., congruent) cardiac feedback, elicited a decrease or increase either in the perception of pain or in the actual cardiac frequency recorded over the anticipation of the nociceptive stimulus. No change in the incongruent feedback phase relative to the congruent feedback would produce a value of 0. Positive and negative values denote an increase or a decrease, relative to the exposure to the congruent feedback, either in pain ratings or anticipatory cardiac frequency, respectively. All data (i.e., Likert, NPS ratings and HR) were normally distributed (all $p > 0.05$) and analyzed with planned paired sample t-test, separately for each dependant variable, that is Δ Numeric Pain Scale, Δ Likert ratings and Δ heart rate parameters. The alpha criterion of significance of all tests was assumed at $p < 0.05$.

Results

Numeric Pain Scale of Intensity

Figure 2a shows the mean of Δ pain intensity ratings (Numeric Pain Scale ratings) after hearing the incongruent faster and slower exteroceptive feedback, relative to congruent feedback baseline. Participants' mean values of Δ pain intensity ratings after faster vs. slower cardiac feedback were compared with a paired sample t-test. The results revealed that participants' perception of pain intensity increased after the exposure to the faster (*mean* 0.10, *SD* 0.23) vs. slower (*mean* -0.01, *SD* 0.16) cardiac feedback, $t(33) = 3.33$, $p = .002$, $d = .59$ (**Figure 2a**). When compared to congruent feedback with additional simple t-tests, significant differences emerged for faster feedback, $t(33) = 2.66$, $p = .01$, $d = .377$, but not for the slower feedback, which showed a slight numerical decrease, $t(33) = 0.47$, $p = .63$, $d = .034$ (not shown).

Pain Unpleasantness Ratings Scale

The Δ pain unpleasantness ratings after the exposure to the slower and faster cardiac feedback, are shown in **Figure 2b**. Mean Δ pain unpleasantness ratings were analysed analogously. A paired sample t-test showed that hearing a faster vs. slower cardiac frequency affected pain unpleasantness ratings, $t(33) = 2.77$, $p = .009$, $d = .51$, such that Δ pain unpleasantness ratings were higher after faster feedback (*mean* 0.083, *SD* 0.15) than slower cardiac feedback (*mean* 0.005, *SD* 0.14) (**Figure 2b**). When compared to congruent feedback with simple t-tests, significant differences emerged for faster feedback, $t(33) = 3.045$, $p = .004$, $d = .512$, but not for the slower feedback, which showed a numerical slight decrease $t(33) = 0.206$, $p = .83$, $d = 0.064$ (not shown).

Real Heartrate

The Δ heart rate acquired over the exposure to the slower and faster cardiac feedback, relative to thecongruent feedback, is shown in **Figure 2c**. The paired sample t-test showed that, relative to the congruent cardiac feedback, participants' real heart rate significantly decreased when hearing the faster (*mean* -0.007, *SD* 0.020) compared to the slower feedback (*mean* -0.02, *SD* 0.011), $t(33) = 2.07$, $p = .045$, $d = .36$ (**Figure 2c**). When compared with congruent feedback, significant heart rate differences emerged for faster feedback, $t(33) = 2.28$, $p = .032$, $d = 0.21$, but not for the slower feedback, which showed a slight numerical decrease $t(33) = 0.92$, $p = 0.36$, $d = .05$ (not shown).

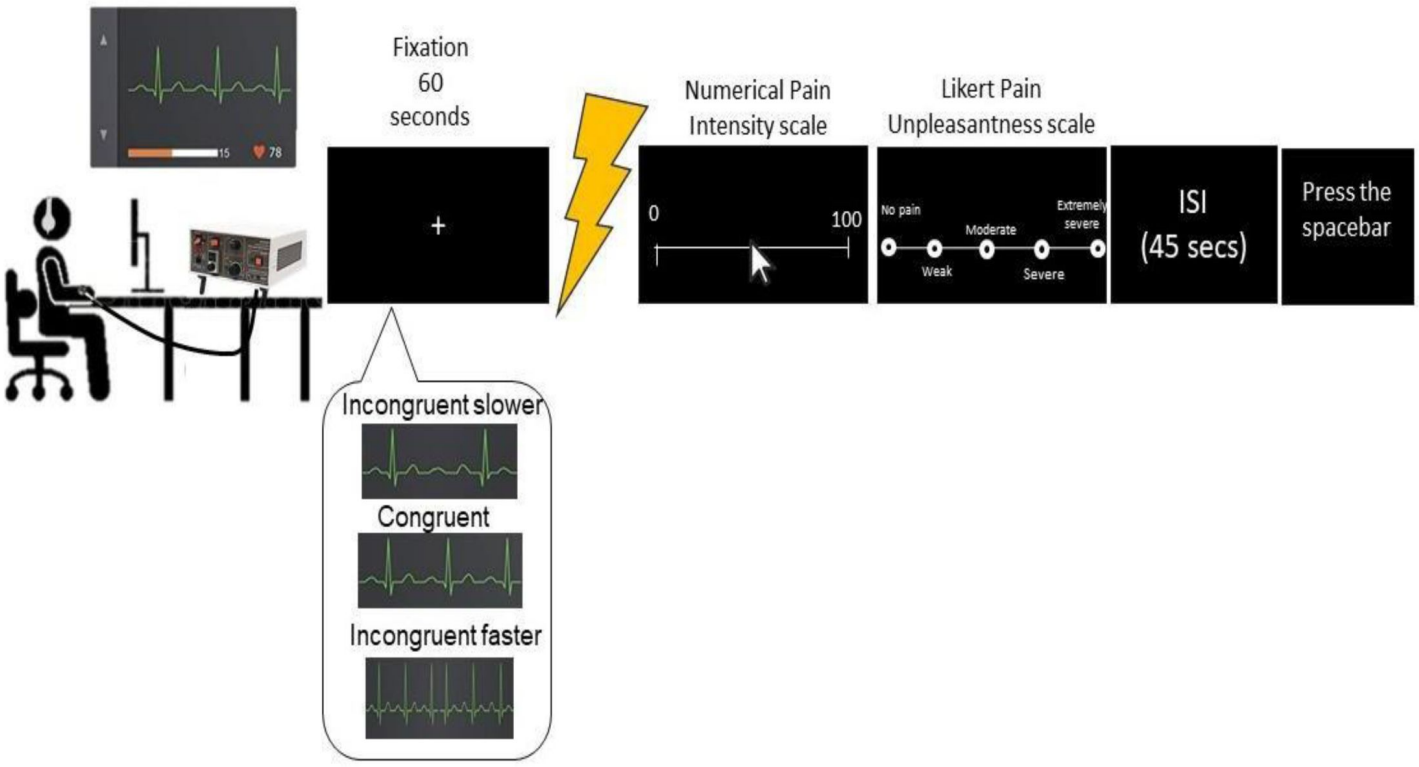

Figure 1.

Trial timeline of the experiment.

Participants are seated with the electrodes of both the electrical stimulation and the ECG attached. Each trial starts with a fixation cross (60 seconds), after which the noxious stimulation is administered and the pain intensity (i.e., Numerical Rating Scale) and unpleasantness (i.e., Likert scale) ratings are collected. After each trial, a pause screen of 45 seconds was shown (i.e., ISI, interstimulus interval), after which participants proceeded to the next trial by pressing the spacebar. The trial timeline was identical for both the no-feedback and feedback phases, with the only exception that in the feedback phase participants were provided with the acoustic feedback (i.e., slower, faster, congruent) about their HR, reproduced for the whole fixation period (60 seconds) preceding the shock.

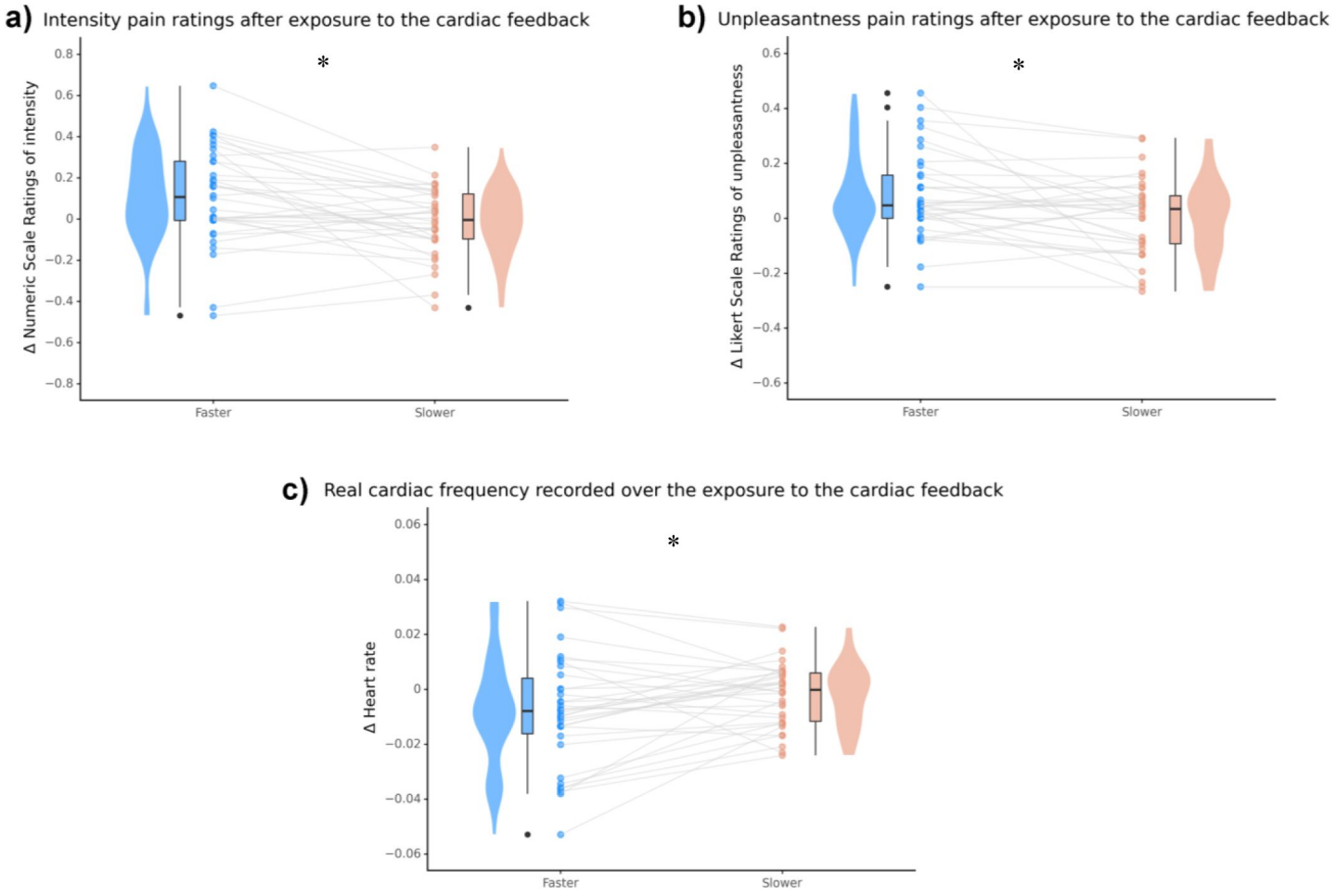

Figure 2.

a Intensity pain ratings (Numeric Pain Scale) **b** Unpleasantness ratings (5-points Likert Scale) **c** Real cardiac frequency. Values consist of the central tendency of change of pain intensity (a), unpleasantness (b) and heart rate (c) associated with the exposure to the faster vs. slower cardiac feedback, relative to the congruent feedback. Values of zero on the vertical axis would represent no change relative to the exposure to the veridical congruent feedback. Positive and negative values would represent an increase and a decrease, respectively. The plot consists of a violin plot, a boxplot, and datapoints. In the boxplot, the line dividing the box represents the median of the data, the ends represent the upper/lower quartiles, the extreme lines represent the highest and lowest values. The code for plot visualization has been adapted from van Langen, 2020.

Body Perception Questionnaire

The Short form Body Perception Questionnaire (Poli et al., 2021) administered at the end of the experiment allowed us to explore whether individual differences in body awareness and supradiaphragmatic reactivity were related to the extent to which participants developed (1) the perceptual illusion of pain (2) the physiological changes in their cardiac frequency. Overall, the average score obtained at the Body awareness subscale and Supradiaphragmatic subscale was 5.22 (*SD*= 1.62) and 2.05 (*SD*= 1.96), respectively. Each participant's score was correlated with their level of Δ pain intensity, Δ pain unpleasantness ratings and Δ heart rate obtained in the faster feedback phase, which was key driver of effects, as seen also in prior research (Valin, 1996; Iodice et al 2019).

Pearson's correlation showed no association between Δ heart rates recorded over the faster feedback phase relative to the congruent feedback and individual's Body awareness subscale and Supradiaphragmatic subscale scores (all $p > 0.05$). Correlating individual's Body awareness subscale and Supradiaphragmatic subscale scores with individual's Δ pain unpleasantness did not show any association between the variables (all $p > 0.05$). Individuals' Δ pain intensity ratings did not show any association with their Body awareness subscale scores ($p > 0.05$), but a negative correlation with the Supradiaphragmatic Reactivity (SUP) scale score (r = -.36, $p = .033$), such that higher Δ pain intensity ratings were associated with lower BPQ scores. This relationship however does not survive Bonferroni correction ($p > 0.025$).

Experiment 2

Experiment 1 established that false accelerated cardiac feedback induced both an illusory increase in the perception of pain and a modulation in the pain-anticipatory related cardiac state (i.e., heart rate) towards the expected level of the noxious stimulus, based on the frequency rate of the cardiac feedback. Experiment 2 tests whether the same perceptual and physiological changes are observed if participants are exposed to an accelerated non-interoceptive feedback (i.e., unrelated to biological human sounds), which should be less likely to induce expectations of threat. To address this question, we substituted the interoceptive cardiac feedback with an exteroceptive tone but kept the experiment otherwise identical. Thus, as in Experiment 1, participants' pain intensity (i.e., Numeric Pain Scale), unpleasantness (i.e., Likert scale) ratings and cardiac frequency (i.e., ECG) were collected both in a no-feedback as well as in a feedback phase, which could be either congruent, faster or slower than participants' individual heartrate recorded over the no-feedback phase. We reasoned that participants would have no expectation that an external acoustic sound signals a preparation of their body to a threatening, high painful stimulus. Consequently, perceptual and cardiac modulations associated to the feedback manipulation should be reduced over the exposure to the faster exteroceptive sound.

Methods

Participants

A sensitivity analysis with G*Power 3.1 (Faul et al., 2007) showed that a sample size of 29 provides .90 power to detect effects with Cohen's d =.62. (SESOI of δ = 0.37). Thirty-five participants (mean age 25.17, SD= 4.02, 23 women) were recruited from Gabriele D'Annunzio University and the wider community. All were right-handed with normal or corrected-to-normal vision. As in Experiment 1, exclusion criteria for taking part were self-reported chronic and acute pain, neurological disease, serious cardiovascular disease (i.e., any type of disease involving the heart or blood vessels that might result in life-threatening medical emergencies, e.g., arrhythmias, infarct, stroke), or conditions that could potentially interfere with pain sensitivity (e.g., drug intake or skin

diseases). Participants were asked to either not drink coffee or smoke cigarettes in the 60 minutes preceding the experiment. All gave written informed consent,were unaware of the purposes of the study, and were fully debriefed about it at the end of the experiment. Ethical approval from the local ethics board was obtained.

As in Experiment 1, participants were excluded if their correlation between the desired five levels of the nociceptive stimulus intensity and their ratings over the no-feedback condition was below r=0.75, suggesting insensitivity to the varying nociceptive degrees of the electrical stimulus. Five participants were excluded with this criterion. Moreover, participants were excluded if, for any reason, they linked the exteroceptive sound to a simulation of an interoceptive, cardiac acoustic feedback, in their post-experiment debriefing. One additional participant was excluded with this criterion. Hence, the final sample size was 29.

Apparatus and Stimuli

The apparatus and stimuli were the same as Experiment 1. The only difference regarded the selectionof the tone used for the creation of the feedback. Instead of using a single heartbeat, the sound was asingle percussion obtained by knocking two woods, gathered from *https://freesound.org* and manipulated in Audacity. The feedback audio was then created in MATLAB (R2020a), repeating the single tone according to the desired frequency (see *Procedure*).

Procedure

The procedure used in Experiment 2 was the same as Experiment 1, with the only exception that thesound used for the feedback was an exteroceptive, instead of interoceptive (i.e., cardiac) tone.

Data Analysis

Data analysis was identical to Experiment 1. Additionally, equivalence tests (i.e., TOST 'two one-sided t-tests' (TOST) procedure, (Lakens, 2017; Lakens et al., 2018) were performed for each variable (i.e., Δ pain unpleasantness and intensity ratings, Δ heart rate). Equivalence tests investigate whether the hypothesis that there are effects extreme enough to be considered meaningful can be rejected. We performed equivalence tests to examine whether the effect of feedback on pain-anticipatory heart rate and pain ratings was at least as extreme as the *smallest effect size of interest* (SESOI). If differences in our variables of interest at least as extreme as the equivalence bounds (i.e. here in standardized effect sizes) can be rejected in two-one sided tests (also known as one-tailed tests; i.e., the TOST procedure), we concluded that either pain ratings or pain-anticipatory heart rate in relation to the exposure to faster vs. slower feedback ratings are statistically equivalent, meaning the difference between our condition of interest (i.e. faster vs. slower feedback) is smaller than what is considered meaningful and statistically falls within the interval indicated by the equivalence bounds.

Results

Numeric Pain Scale of Intensity

Figure 3a shows the mean of Δ pain intensity ratings given after hearing the incongruent faster vs. slower exteroceptive feedback, relative to the congruent feedback baseline. Data were analysed as in Experiment 1, using a paired t-test to evaluate whether pain ratings differed after hearing the incongruent faster and slower feedback. In contrast to Experiment 1, mean Δ pain intensity ratings were not affected by feedback frequency, $t(28) = .65$, $p = .51$, $d = .12$ (**Figure 3a**). TOST procedure (Lakens, 2017) indicated that the observed effect size ($d = .12$) was significantly within the equivalence bounds of $\Delta L = –.57$ and $\Delta U = .57$, $p = .011$. Relative to congruent feedback,

intensity ratings were increased for both faster and slower feedback, even though the difference was robust only for the faster feedback, $t(28) = 2.18$, $p = 0.037$, $d = 0.28$, not the slower cardiac feedback, $t(28) = 1.58$, $p = 0.12$, $d = 0.22$.

Pain Unpleasantness Ratings Scale

Figure 3b shows the mean Δ pain unpleasantness ratings given after the exposure to the incongruent faster vs. slower cardiac feedback, relative to the congruent feedback. A paired sample t-test revealed no significant difference between Δ pain unpleasantness ratings after slower vs. faster feedback, $t(28) = 1.17$, $p = .24$, $d = .19$ (**Figure 3b**). TOST procedure (Lakens, 2017) indicated that the observed effect size ($d = .19$) was significantly within the equivalence bounds of $\Delta L = –.57$ and $\Delta U = .57$, $p = .035$. Further simple t-tests showed that, relative to the congruent feedback, differences did neither emerge for faster feedback, $t(28) = 1.51$, $p = .14$, $d = .28$, nor for the slower feedback, $t(28) = .38$, $p = .70$, $d = .06$ (not shown).

Real Heartrate

Figure 3c shows the Δ Heartrate acquired over the exposure to the slower and faster exteroceptivefeedback, relative to the congruent feedback. The paired-sample t-test revealed no significant difference between the exposure to the slower vs. faster exteroceptive feedback, $t(28) = 1.48$, $p = .14$, $d = .26$ (**Figure 3c**). TOST procedure (Lakens, 2017) indicated that the observed effect size ($d = .26$) was significantly within the equivalence bounds of $\Delta L = –.57$ and $\Delta U = .57$, $p = .065$. When heart rate recorded over the exposure to the slower and faster exteroceptive feedback was compared to the cardiac frequency acquired over the congruent feedback, no significant differences emerged for faster feedback, which showed a slight numerical decrease $t(28) = .71$, $p = .48$, $d = .06$, but for the slower feedback, which showed a robust decrease $t(28) = -2.189$, $p = .037$, $d = .19$ (not shown).

Additional comparison analysis between experiments

To address whether the perceptual and cardiac biases were differently modulated by the exteroceptive vs. interoceptive sound reproduced by the feedback, we directly compared the changes in either the anticipatory cardiac response or the reported levels of pain intensity and unpleasantness elicited by both feedback manipulations. We predicted that (1) the increase in both pain unpleasantness and intensity ratings observed after hearing the incongruent faster vs. slower feedback, and (2) the decrease in the real cardiac frequency observed over the exposure to the incongruent faster vs. slower feedback, were enhanced in the group of participants exposed to the interoceptive cardiac sound (Experiment 1), relative to the one that received the exteroceptive tone (Experiment 2). Such findings would demonstrate that perceptual and cardiac changes linked to the exposure to the accelerated feedback was largely associated to the generation of specific interoceptive expectations conveyed by simulated cardiac streams, which provided (false) information about the state of the body in relation to a threat.

To test this hypothesis, the Δ of pain ratings and heart rate parameters obtained after the exposure to the interoceptive (Experiment 1) and exteroceptive (Experiment 2) feedback, were entered into a 2 X 2 mixed measures analysis of variance (ANOVA) for the Δ Numeric Pain Scale ratings, Δ Likert ratings and Δ heart rate separately, with Experiment (Cardiac feedback vs. Exteroceptive feedback) as a between-subjects factor, and Feedback frequency (Faster vs. Slower) as within-subjects factors. Our prediction is that either the increase in the perceived pain intensity (Numeric Pain Scale) and unpleasantness (Likert Scale) or the heart rates decrease observed over the exposure to the faster vs. slower feedback will be reduced when participants were exposed to the cardiac feedback (i.e., Experiment 1), relative to the exteroceptive sound (i.e., Experiment 2). Interactions with Experiment will therefore reveal whether groups differ in how much either perceptual or cardiac frequency changes are biased by the type of sound reproduced by the manipulated feedback, and not simply the frequency rate of the acoustic feedback.

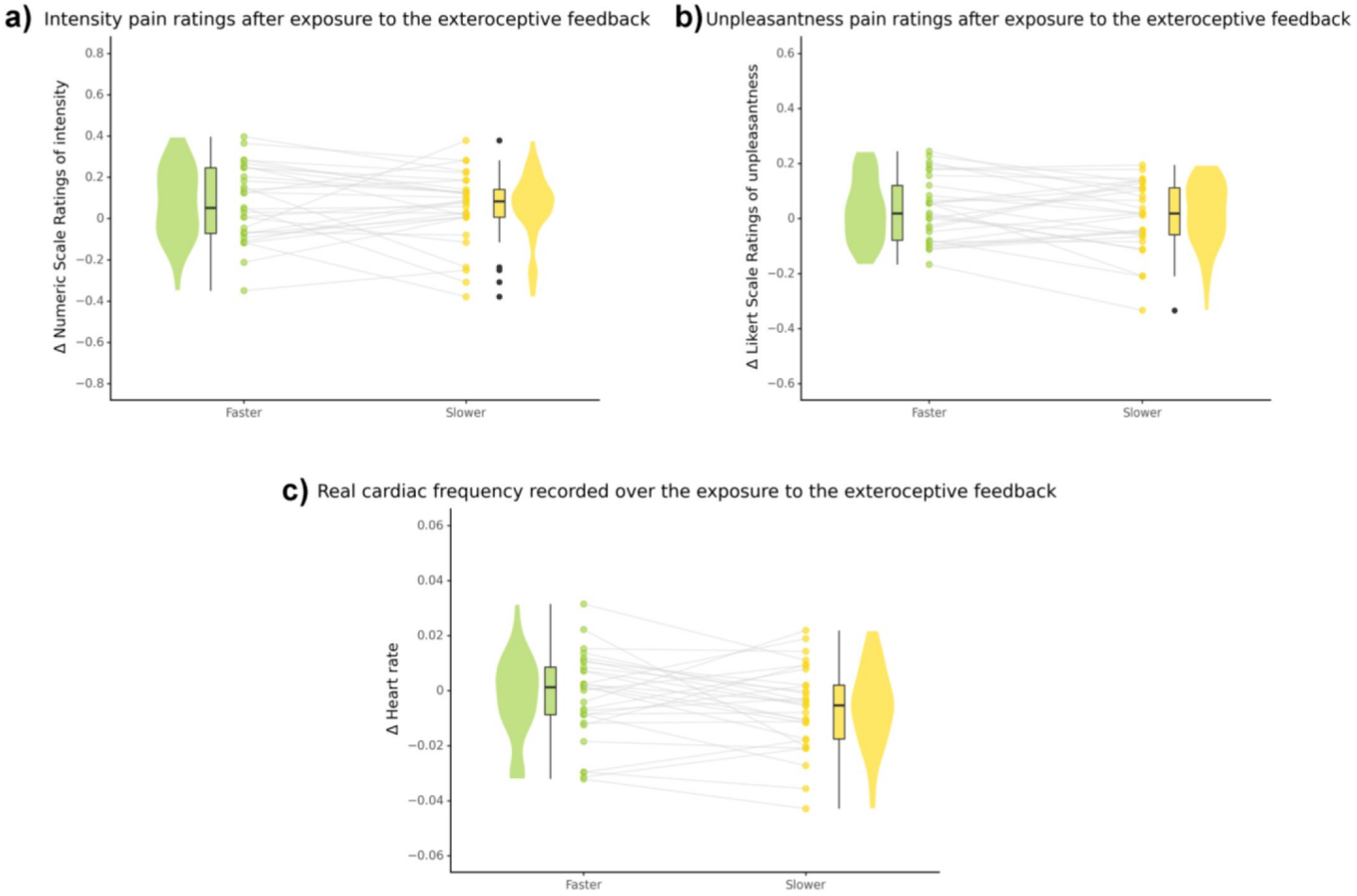

Figure 3.

a Intensity pain ratings (Numeric Pain Scale) **b** Unpleasantness ratings (5-points Likert Scale) **c** Real cardiac frequency. Values consist of central tendency of the change of pain intensity (a), unpleasantness (b) and heart rate (c) associated with the exposure to the faster vs. slower exteroceptive feedback, relative to the congruent feedback. Values of zero on the vertical axis would represent no change relative to the exposure to the veridical congruent feedback. Positive and negative values would represent an increase and a decrease, respectively. The plot consists of a violin plot, a boxplot, and datapoints. In the boxplot, the line dividing the box represents the median of the data, the ends represent the upper/lower quartiles, and the extreme lines represent the highest and lowest values. The code for plot visualization has been adapted from van Langen, 2020.

Numeric Pain Scale

The 2×2 ANOVA revealed a main effect of Feedback frequency $F(1,61) = 8.28$, $p = 0.006$, $\eta p^2 = 0.12$. Participants' reported levels of pain intensity were generally higher after exposure to the faster, relative to the slower feedback. Importantly, and as predicted, this main effect was qualified by an interaction of Feedback frequency and Experiment, $F(1,61) = 4.04$, $p = 0.04$, $\eta p^2 = 0.062$. The faster feedback affected the perceptual bias more strongly in the Experiment 1 than in Experiment 2. Specifically, when participants were exposed to the faster, but not slower, cardiac interoceptive sound, their perceived and reported level of pain intensity was generally higher. This effect was not induced by sound reproducing an exteroceptive tone.

Pain Unpleasantness Ratings Scale

Results revealed a main effect of Feedback frequency $F(1,61) = 8.11$, $p = 0.006$, $\eta p^2 = 0.117$, showing that after the exposure to the faster, relative to the slower feedback, participants generally reported higher levels of perceived unpleasantness associated to the noxious stimulus. This main effect was not qualified by interactions with Experiment ($p = 0.13$), showing that the specific type of sound reproduced by the acoustic feedback (cardiac vs. exteroceptive) did not differently modulated the perceived levels of pain unpleasantness associated to the nociceptive stimulus.

Heart rate

The 2×2 ANOVA showed no main effect of Feedback frequency $F < 1$. Importantly, the interaction Feedback by Experiment was significant $F(1,61) = 6.253$, $p = 0.015$, ηp2 = 0.093, showing that the exposure to the faster vs. slower cardiac feedback generally decreases heartrates, while listening to the exteroceptive faster vs. slower exteroceptive feedback generally increases participants' cardiac frequency.

General Discussion

Interoceptive inference and the Embodied Predictive Coding frameworks (Barrett, 2017; Barrett & Simmons, 2015; Pezzulo, 2014; A. K. Seth, 2013; A. K. Seth & Friston, 2016) understand interoception as a reflection of the brain's probabilistic inferences, through which it estimates and controls crucial physiological and homeostatic variables, by combining incoming sensory information from multiple modalities. In line with such views, expectations about pain should be integrated, in a Bayesian manner, with other interoceptive sources, here represented by cardiac streams reproduced with the acoustic feedback that generated predictions of increased threat levels associated with the forthcoming stimulus. Unbeknownst to participants, before the administration of the same intensity noxious stimuli, we varied the frequency of the cardiac feedback, manipulating the speed of what they thought was their ongoing heart rate. This sufficed to induce misleading expectations about the upcoming level of nociception associated with the stimulation.

In line with predictive models, reducing the gap between expected and actual interoceptive information can be achieved either by changing one's perceptual state to encompass the new information, or by actively changing the body in response to the unexpected input, by engaging for example autonomous reflexes (i.e., perceptual and active inference, Parr et al., 2022, Friston, 2005; 2010; for a full discussion on interoception, see Ainley et al., 2016, Paulus et al., 2019). If so, then sensing an accelerated heartrate when anticipating pain might have two consequences. First, it may falsely lead participants to expect, and then perceive, a more intense pain stimulus then is really delivered. Second, it may induce changes in the internal states themselves, compensating for the perceived changes in heartrate by actually up-down-regulating one's heartrate, towards the expected decreasing orienting cardiac response when expecting threatening stimuli (Lykken et al., 1972; Taggart et al., 1976; Bradley et al., 2005; Bradley et

al., 2008; Colloca et al., 2012; Tracy et al., 2017). This inferential process has been demonstrated in various computational models of cardiac (Smith et al., 2020) and gastrointestinal (Smith et al., 2021) interoception, thermoregulation (Tschantz et al., 2022), and psychopathological conditions, such as anorexia nervosa (Barca & Pezzulo, 2020), panic disorder (Maisto et al., 2021), depression (Barrett et al., 2016; Stephan et al., 2016), and others (Paulus et al., 2019).

The results of Experiment 1 provide evidence for both components of the hypothesized response. They show, first, that faster cardiac feedback induces an illusory perception of increased unpleasantness and intensity of subsequent pain stimuli. Thus, as predicted, the mismatch between people's expectations and the actual input (i.e., expecting a high level of pain but having equal nociceptive intensities of the stimulus) led to changes in the perception of pain, which reflected the *expected* input, more than the real changes that should be evoked by identical noxious stimulus. Secondly, the results showed that faster cardiac feedback also changed participants' real heart rate. When hearing the faster feedback, the real heartrate tended to decrease, assuming the pattern of anticipatory response typically enacted when humans prepare to face a threatening stimulus (Lykken et al., 1972; Taggart et al., 1976; Bradley et al., 2005; Bradley et al., 2008; Colloca et al., 2006; Tracy et al., 2017). This evidence supports the hypothesis that not only interoceptive states modulate inferences, and then interoceptive perception, but the converse is also true: inference dynamics can modify or produce new internal states, to the extent that the actual cardiac frequency rate decreased as it would have done over the anticipation of a real threat.

Decreased cardiac activity in response to threat has been shown in both human and non-human species (for a review, see Livermore et al., 2021; Roelofs, 2017; Vila et al., 2007). More broadly, cardiac deceleration it is observed during highly salient events and attentive preparation (Jennings et al., 2009; Jennings & van der Molen, 2005; Van der Veen et al., 2000) and it is considered an evolutionarily-conserved, adaptive response that allows the organism to orient attention and enhance information processing and action preparation (Hashemi et al., 2019; Klaassen et al., 2021; Lojowska et al., 2015). Blending well with early cardiac reflexes literature, under which cortical excitation/inhibition is modulated by down- or up-regulating cardiac activity in order to engage or disengage, respectively, with salient stimuli (Lacey, 1970), recent proposals frames cardiac deceleration under a Bayesian inference approach. Under these views, the cardiac deceleration mechanism allows to adjust precision of sensory evidence accumulation relative to precision of bodily information, optimising perception and action (Skora et al., 2022). Thus, decelerated cardiac activity observed over the exposure to the faster feedback may reflect an autonomic adjustment to prioritize incoming noxious input information in light of the expectation of the threatening painful event.

To the best of our knowledge, this is the first study to successfully demonstrate both active and perceptual inference consequences of false interoceptive feedback, supporting the notion that, based on prior knowledge and expectations, the brain actively implements the interoceptive consequences that have been predicted (for a full discussion, see Barrett and Simmons, 2015; Pezzulo, 2014; Seth and Friston, 2016). Along similar lines, it has been demonstrated that is possible to generate predictions along the body dimension, inducing both active and perceptual inference. For example, in one of the most studied body illusion, the "rubber hand illusion", the discrepancy between the seen and felt touch is reduced either by changing perception, such that individuals come to experience a sense of ownership over the rubber hand and misperceive the actual location of their hand (Botvinick & Cohen, 1998), or by active processes, such as performing automatic compensative movements (e.g., Asai, 2015) or engaging autonomic reflexes (e.g, Hohwy and Paton, 2010; Moseley et al., 2008). Interestingly, both perceptual and active inference during the rubber hand illusion can be induced also by expectation rather than experience of a tactile event (Ferri et al., 2013).

Our findings greatly expand upon this existing research, suggesting that, as it happens for bodily signals, the brain may analogously generate top-down interoceptive predictions with either perceptual or active consequences. Building upon emerging models that highlight the significance of active inference in addressing multisensory conflicts or accomplishing goals (Maselli et al., 2022), these findings have the potential to broaden the scope of these perspectives, encompassing domains ranging from motor control to interoceptive processes. In this regard, interoceptive and exteroceptive aspects of the body may draw upon similar predictive mechanisms, which involve the integration of diverse streams of information from multiple senses to form a central representation of their essential variables. This is in line with the emerging idea that the brain maintains an interoceptive schema for (optimal) multimodal integration. Paralleling the body schema (Head & Holmes, 1911), the interoceptive schema consists in a central representation of interoceptive variables (e.g., body temperature, cardiac activity etc.) along with prior assumptions or "set points" for these variables. This internal model would support homeostatic and allostatic regulation by optimally weighting multiple (i.e., proprioceptive, interoceptive, exteroceptive) streams of information to predict incoming interoceptive signals (Barca & Pezzulo, 2020; Iodice et al., 2019; Schoeller et al., 2022; Tschantz et al., 2022). If such a schema regulates our interoceptive states, the manipulation of illusions in this domain would serve as a unique framework to test it.

Not surprisingly, we did not find any counterpart of either the illusion of pain, or of the associated autonomous response, when providing participants with slower cardiac feedback. This result is in line with previous findings (e.g., (Iodice et al., 2019) that highlighted a similar asymmetry in the illusory perception of effort after a cardiac feedback manipulation. As in the current study, participants did not underestimate effort when provided with slower feedback, but they consistently overestimated effort levels after receiving faster cardiac feedback. Following this prior study, we interpret this result as a protective strategy through which predictive processes aim at promoting adaptive outcomes. Underestimating, but not overestimating pain constitutes a risk for the organism, as it can turn into a maladaptive behaviour and lead to dangerous consequences.

Importantly, both perceptual and cardiac frequency changes after faster (vs. slower) feedback were dramatically reduced when the heartbeat tone was replaced by an exteroceptive sound in Experiment 2. This finding supports the hypothesis that such perceptual and physiological modulations were specifically tied to the interoceptive streams reproduced by the feedback, which provided evidence of the current state of the body in preparation for a potential upcoming (threatening) stimulus. Therefore, varying the frequency of an external sound that is not informative of the current state of the body or related to interoceptive streams, should not induce any expectation about the nociceptive level of the stimulus. In other words, while hearing their own cardiac frequency varying may have been interpreted as a signal of their body preparation to a threatening painful event, participants would have no expectation about exteroceptive tone stimuli. Consequently, no discrepancy in the pain unpleasantness and intensity ratings, as well as in participants' actual heart rates, were observed in Experiment 2, when participants were exposed to the faster, relative to the incongruent slower feedback, and the modulations induced in pain intensity and heart rates were significantly reduced.

Importantly, perceptual and autonomic changes were induced by false feedback about participants' internal state, in contrast to prior work that manipulated expectations mainly with exteroceptive cues (Atlas et al., 2010; Colloca et al., 2006; Jepma et al., 2018; Tracy et al., 2017; Wiech et al., 2014), in line with the proposal that interoceptive inferences might integrate prior knowledge and all available sensory, proprioceptive and interoceptive signals that describe the state of the body (Iodice et al., 2019; Pezzulo, 2014). In particular, the findings provided here support the notion that pain represents a critical variable within the predictive coding scheme, and that its estimation exploits prior knowledge and beliefs, and, among others, devotes special attention to cardiac streams from within the body, which can lead us to conclude

that the internal generative model of pain considers heart rate in the likelihood model. In turn, the estimate of pain and of other physiologically relevant variables might be key for allostatic functions and adaptive, energy-efficient regulation by the brain (Barrett et al., 2016).

Furthering the underlying mechanisms of illusions provide a precious opportunity to learn about the role of predictions in shaping our understanding of the world around and inside us, offering the occasion to observe it through the lenses of the internal generative models that guide perceptions and actions. This evidence provides a point of departure to develop a full picture of predictive interoceptive dynamics, as which are the interoceptive channels that the brain monitors to estimate crucial variables, or how predictive processes orchestrate all different streams of information within the embodied multisensory sphere. In this view, it is possible to create novel illusions and manipulate the precision of signals coming from different channels (i.e., proprioceptive, interoceptive, exteroceptive) to study whether the brain might weight and integrate specific sources of information to predict precise homeostatic variables.

A central assumption in predictive models is that predictions and associated prediction-error are represented in terms of precision, wherein 'precision' refers to the salience and reliability of each probability distribution (Ainley et al., 2016; Feldman and Friston, 2010; Hohwy, 2012; Palmer et al., 2019; Parr et al., 2022; Seth and Friston, 2016; Yon and Frith, 2021). In this regard, future studies may investigate whether the reliability of people's expectations about the link between their heart rate and threat anticipation underpins the development of the interoceptive illusion. This might involve self-report measures that properly investigate and quantify participants' beliefs, and how they manifest in perceptual or bodily changes. Exploring the degree of certainty of priors may constitute a testing bed to investigate the role of precision in weighting the available information that arises from different modalities. Future research may explore whether the illusion in pain perception might be altered by changing people's prior knowledge about the link between their cardiac frequency and the experience of pain (e.g., providing participants some prior knowledge about potential decreases in heart rate in anticipation of pain). This may shed light on whether perceptual biases in the experience of pain are associated to overlearned priors that do not update to incoming sensory data, or, instead, whether it is possible to directly act on the perceptual illusion by changing prior knowledge. This would have far-reaching implications, resulting in the striking consequence that is possible to modify the perception of our internal milieu, but also impact autonomic states by simply reconfiguring individuals' beliefs and knowledge. Such findings would hold profound consequences for understanding and potentially intervening in psychopathological conditions influenced by distorted perception and maladaptive cognitive biases.

In this regard, the contribution of the study of illusions offers important insights not only for a converging model of brain functioning under the principle of optimal predictive architectures, but it also provides implications for understanding psychopathology in terms of aberrant predictions and compounding allostatic consequences (for a full discussion, see Barrett & Simmons, 2015), based on the inability to accurately predict and revise, when needed, prior – interoceptive - beliefs.

In this view, the illusion of pain highlighted here, as well as other interoceptive illusions, may constitute an opening window on the understanding of disrupted balancing between prior knowledge and incoming sensory information, potentially explaining psychopathological conditions.

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Reviewer #1 (Public Review):

Summary:
I read the paper by Parrotta et al with great interest. The authors are asking an interesting and important question regarding pain perception, which is derived from predictive processing accounts of brain function. They ask: If the brain indeed integrates information coming from within the body (interoceptive information) to comprise predictions about the expected incoming input and how to respond to it, could we provide false interoceptive information to modulate its predictions, and subsequently alter the perception of such input? To test this question, they use pain as the input and the sounds of heartbeats (falsified or accurate) as the interoceptive signal.

Strengths:
I found the question well-established, interesting, and important, with important implications and contributions for several fields, including neuroscience of prediction-perception, pain research, placebo research, and health psychology. The paper is well-written, the methods are adequate, and the findings largely support the hypothesis of the authors. The authors carried

out a control experiment to rule out an alternative explanation of their finding, which was important.

Weaknesses:
I will list here one theoretical weakness or concern I had, and several methodological weaknesses.

The theoretical concern regards what I see as a misalignment between a hypothesis and a result, which could influence our understanding of the manipulation of heartbeats, and its meaning: The authors indicate from prior literature and find in their own findings, that when preparing for an aversive incoming stimulus, heartbeats *decrease*. However, in their findings, manipulating the heartbeats that participants hear to be slower than their own prior to receiving a painful stimulus had *no effect* on participants' actual heartbeats, nor on their pain perceptions. What authors did find is that when listening to heartbeats that are *increased* in frequency - that was when their own heartbeats decreased (meaning they expected an aversive stimulus) and their pain perceptions increased.

This is quite complex - but here is my concern: If the assumption is that the brain is collecting evidence from both outside and inside the body to prepare for an upcoming stimulus, and we know that *slowing down* of heartbeats predicts an aversive stimulus, why is it that participants responded in a change in pain perception and physiological response when listened to *increased heartbeats* and not decreased? My interpretation is that the manipulation did not fool the interoceptive signals that the brain collects, but rather the more conscious experience of participants, which may then have been translated to fear/preparation for the incoming stimulus. As the authors indicate in the discussion (lines 704-705), participants do not *know* that decreased heartbeats indicate upcoming aversive stimulus, and I would even argue the opposite - the common knowledge or intuitive response is to increase alertness when we hear increased heartbeats, like in horror films or similar scenarios. Therefore, the unfortunate conclusion is that what the authors assume is a manipulation of interoception - to me seems like a manipulation of participants' alertness or conscious experience of possible danger. I hope the (important) distinction between the two is clear enough because I find this issue of utmost importance for the point the paper is trying to make. If to summarize in one sentence - if it is decreased heartbeats that lead the brain to predict an approaching aversive input, and we assume the manipulation is altering the brain's interoceptive data collection, why isn't it responding to the decreased signal? --> My conclusion is, that this is not in fact a manipulation of interoception, unfortunately.

I will add that the control experiment - with an exteroceptive signal (knocking of wood) manipulated in a similar manner - could be seen as evidence of the fact that heartbeats are regarded as an interoceptive signal, and it is an important control experiment, however, to me it seems that what it is showing is the importance of human-relevant signals to pain prediction/perception, and not directly proves that it is considered interoceptive. For example, it could be experienced as a social cue of human anxiety/fear etc, and induce alertness.

Several additional, more methodological weaknesses include the very small number of trials per condition - the methods mention 18 test trials per participant for the 3 conditions, with varying pain intensities, which are later averaged (and whether this is appropriate is a different issue). This means 6 trials per condition, and only 2 trials per condition and pain intensity. I thought that this number could be increased, though it is not a huge concern of the paper. It is, however, needed to show some statistics about the distribution of responses, given the very small trial number (see recommendations for authors). The sample size is also rather small, on the verge of "just right" to meet the required sample size according to the authors' calculations. Finally, and just as important, the data exists to analyze participants' physiological responses (ECG) after receiving the painful stimulus - this could support the authors' claims about the change in both subjective and objective responses to pain. It could

also strengthen the physiological evidence, which is rather weak in terms of its effect. Nevertheless, this is missing from the paper.

I have several additional recommendations regarding data analysis (using an ANOVA rather than multiple t-tests, using raw normalized data rather than change scores, questioning the averaging across 3 pain intensities) - which I will detail in the "recommendations for authors" section.

Conclusion:
To conclude, the authors have shown in their findings that predictions about an upcoming aversive (pain) stimulus - and its subsequent subjective perception - can be altered not only by external expectations, or manipulating the pain cue, as was done in studies so far, but also by manipulating a cue that has fundamental importance to human physiological status, namely heartbeats. Whether this is a manipulation of actual interoception as sensed by the brain is - in my view - left to be proven.
Still, the paper has important implications in several fields of science ranging from neuroscience prediction-perception research, to pain and placebo research, and may have implications for clinical disorders, as the authors propose. Furthermore, it may lead - either the authors or someone else - to further test this interesting question of manipulation of interoception in a different or more controlled manner.

I salute the authors for coming up with this interesting question and encourage them to continue and explore ways to study it and related follow-up questions.

Reviewer #2 (Public Review):

In this manuscript, Parrotta et al. tested whether it is possible to modulate pain perception and heart rate by providing false HR acoustic feedback before administering electrical cutaneous shocks. To this end, they performed two experiments. The first experiment tested whether false HR acoustic feedback alters pain perception and the cardiac anticipatory response. The second experiment tested whether the same perceptual and physiological changes are observed when participants are exposed to a non-interoceptive feedback. The main results of the first experiment showed a modulatory effect for faster HR acoustic feedback on pain intensity, unpleasantness, and cardiac anticipatory response compared to a control (acoustic feedback congruent to the participant's actual HR). However, the results of the second experiment also showed an increase in pain ratings for the faster non-interoceptive acoustic feedback compared to the control condition, with no differences in pain unpleasantness or cardiac response.

The main strengths of the manuscript are the clarity with which it was written, and its solid theoretical and conceptual framework. The researchers make an in-depth review of predictive processing models to account for the complex experience of pain, and how these models are updated by perceptual and active inference. They follow with an account of how pain expectations modulate physiological responses and draw attention to the fact that most previous studies focus on exteroceptive cues. At this point, they make the link between pain experience and heart rate changes, and introduce their own previous work showing that people may illusorily perceive a higher cardiac frequency when expecting painful stimulation, even though anticipating pain typically goes along with a decrease in HR. From here, they hypothesize that false HR acoustic feedback evokes more intense and unpleasant pain perception, although the actual HR actually decreases due to the orienting cardiac response. Furthermore, they also test the hypothesis that an exteroceptive cue will lead to no (or less) changes in those variables. The discussion of their results is also well-rooted in the existing bibliography, and for the most part, provides a credible account of the findings.

The main weaknesses of the manuscript lies in a few choices in methodology and data analysis that hinder the interpretation of the results and the conclusions as they stand. The

first peculiar choice is the convoluted definition of the outcomes. Specifically, pain intensity and unpleasantness are first normalized and then transformed into variation rates (sic) or deltas, which makes the interpretation of the results unnecessarily complicated. This is also linked to the definitions of the smallest effect of interest (SESOI) in terms of these outcomes, which is crucial to determining the sample size and gauging the differences between conditions. However, the choice of SESOI is not properly justified, and strangely, it changes from the first experiment to the second.

Furthermore, the researchers propose the comparison of faster vs. slower delta HR acoustic feedback throughout the manuscript when the natural comparison is the incongruent vs. the congruent feedback. This could be influenced by the fact that the faster HR exteroceptive cue in experiment 2 also shows a significant modulatory effect on pain intensity compared to congruent HR feedback, which puts into question the hypothesized differences between interoceptive vs. exteroceptive cues. These results could also be influenced by the specific choice of exteroceptive cue: the researchers imply that the main driver of the effect is the nature of the cue (interoceptive vs. exteroceptive) and not its frequency. However, they attempt to generalize their findings using knocking wood sounds to all possible sounds, but it is possible that some features of these sounds (e.g., auditory roughness or loomingness) could be the drivers behind the observed effects. Finally, it is noteworthy that the researchers divided the study into two experiments when it would have been optimal to test all the conditions with the same subjects in a randomized order in a single cross-over experiment to reduce between-subject variability.

Taking this into consideration, I believe that the conclusions are only partially supported by the evidence. Despite of the outcome transformations, a clear effect of faster HR acoustic feedback can be observed in the first experiment, which is larger than the proposed exteroceptive counterpart. This work could be of broad interest to pain researchers, particularly those working on predictive coding of pain.

Reviewer #3 (Public Review):

Summary:

In their manuscript titled "Exposure to false cardiac feedback alters pain perception and anticipatory cardiac frequency", Parrotta and colleagues describe an experimental study on the interplay between false heart rate feedback and pain experience in healthy, adult humans. The experimental design is derived from Bayesian perspectives on interoceptive inference. In Experiment 1 (N=34), participants rated the intensity and unpleasantness of an electrical pulse presented to their middle fingers. Participants received auditory cardiac feedback prior to the electrical pulse. This feedback was congruent with the participant's heart rate or manipulated to have a higher or lower frequency than the participant's true heart rate (incongruent high/ low feedback). The authors find heightened ratings of pain intensity and unpleasantness as well as a decreased heart rate in participants who were exposed to the incongruent-high cardiac feedback. Experiment 2 (N=29) is equivalent to Experiment 1 with the exception that non-interoceptive auditory feedback was presented. Here, mean pain intensity and unpleasantness ratings were unaffected by feedback frequency.

Strengths:

The authors present interesting experimental data that was derived from modern theoretical accounts of interoceptive inference and pain processing.

1. The motivation for the study is well-explained and rooted within the current literature, whereas pain is the result of a multimodal, inferential process. The separation of nociceptive stimulation and pain experience is explained clearly and stringently throughout the text.

2. The idea of manipulating pain-related expectations via an internal, instead of an external cue, is very innovative.

3. An appropriate control experiment was implemented, where an external (non-physiological) auditory cue with parallel frequency to the cardiac cue was presented.

4. The chosen statistical methods are appropriate, albeit averaging may limit the opportunity for mechanistic insight, see weaknesses section.

5. The behavioral data, showing increased unpleasantness and intensity ratings after exposure to incongruent-high cardiac feedback, but not exteroceptive high-frequency auditory feedback, is backed up by ECG data. Here, the decrease in heart rate during the incongruent-high condition speaks towards a specific, expectation-induced physiological effect that can be seen as resulting from interoceptive inference.

Weaknesses:

Additional analyses and/ or more extensive discussion are needed to address these limitations:

1. I would like to know more about potential learning effects during the study. Is there a significant change in Δ intensity and Δ unpleasantness over time; e.g. in early trials compared to later trials? It would be helpful to exclude the alternative explanation that over time, participants learned to interpret the exteroceptive cue more in line with the cardiac cue, and the effect is driven by a lack of learning about the slightly less familiar cue (the exteroceptive cue) in early trials. In other words, the heartbeat-like auditory feedback might be "overlearned", compared to the less naturalistic tone, and more exposure to the less naturalistic cue might rule out any differences between them w.r.t. pain unpleasantness ratings.

2. The origin of the difference in Cohen's d (Exp. 1: .57, Exp. 2: .62) and subsequently sample size in the sensitivity analyses remains unclear, it would be helpful to clarify where these values are coming from (are they related to the effects reported in the results? If so, they should be marked as post-hoc analyses).

3. As an alternative explanation, it is conceivable that the cardiac cue may have just increased unspecific arousal or attention to a larger extent than the exteroceptive cue. It would be helpful to discuss the role of these rather unspecific mechanisms, and how it may have differed between experiments.

4. The hypothesis (increased pain intensity with incongruent-high cardiac feedback) should be motivated by some additional literature.

5. The discussion section does not address the study's limitations in a sufficient manner. For example, I would expect a more thorough discussion on the lack of correlation between participant ratings and self-reported bodily awareness and reactivity, as assessed with the BPQ.
a. Some short, additional information on why the authors chose to focus on body awareness and supradiaphragmatic reactivity subscales would be helpful.

6. The analyses presented in this version of the manuscript allow only limited mechanistic conclusions - a computational model of participant's behavior would be a very strong addition to the paper. While this may be out of the scope of the article, it would be helpful for the reader to discuss the limitations of the presented analyses and outline avenues towards a more mechanistic understanding and analysis of the data. The computational model in [7] might contain some starting ideas.

Some additional topics were not considered in the first version of the manuscript:
1. The possible advantages of a computational model of task behavior should be discussed.
2. Across both experiments, there was a slightly larger number of female participants. Research suggests significant sex-related differences in pain processing [1,2]. It would be interesting to see what role this may have played in this data.
3. There are a few very relevant papers that come to mind which may be of interest. These sources might be particularly useful when discussing the roadmap towards a mechanistic understanding of the inferential processes underlying the task responses [3,4] and their clinical implications.
4. In this version of the paper, we only see plots that illustrate Δ scores, averaged across pain intensities - to better understand participant responses and the relationship with stimulus intensity, it would be helpful to see a more descriptive plot of task behavior (e.g. stimulus intensity and raw pain ratings)

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